Flk2/Flt3 promotes both myeloid and lymphoid development by expanding non-self-renewing multipotent hematopoietic progenitor cells.

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Public Summary:
Activating mutations in the Flk2 receptor are the most commonly found mutations in acute myeloid leukemia's (AML). To determine which blood cell types require a Flk2-expressing stage during their development, we analyzed Flk2-deficient mice. In the absence of Flk2 expression, we observed an impaired ability of stem cells and progenitors to propagate both myeloid and lymphoid cell types. Therefore, Flk2 expression is required to maintain proper cells numbers of all blood cell types.

Scientific Abstract:
Defining differentiation pathways is central to understanding the pathogenesis of hematopoietic disorders, including leukemia. The function of the receptor tyrosine kinase Flk2 (Flt3) in promoting myeloid development remains poorly defined, despite being commonly mutated in acute myeloid leukemia. Here, we investigated the effect of Flk2 deficiency on myelopoiesis, focusing on specification of progenitors between HSC and mature cells. We provide evidence that Flk2 is critical for proliferative expansion of multipotent progenitors (MPP) that are common precursors for all lymphoid and myeloid lineages, including megakaryocyte/erythroid (MegE) cells. Flk2 deficiency impaired the generation of both lymphoid and myeloid progenitors by abrogating propagation of their common upstream precursor. At steady-state, downstream compensatory mechanisms masked the effect of Flk2 deficiency on mature myeloid output, whereas transplantation of purified progenitors revealed impaired generation of all mature lineages. Flk2 deficiency did not affect lineage choice, thus dissociating the role of Flk2 in promoting cell expansion and regulating cell fate. Surprisingly, despite impairing myeloid development, Flk2 deficiency afforded protection against myeloablative insult. This survival advantage was attributed to reduced cell cycling and proliferation of progenitors in Flk2-deficient mice. Our data support the existence of a common Flk2+ intermediate for all hematopoietic lineages and provide insight into how activating Flk2 mutations promote hematopoietic malignancy by non-Flk2-expressing myeloid cells.